REMARKS

In order to expedite the prosecution of the present application, Claim 18 has been canceled and Claim 19 amended to state that the superoxide dismutase combined with gliadin is administered orally. Additionally, in order to find claim language acceptable to the Examiner, Applicants have added two new claim sets. The first claim set, Claims 26-29, is directed to a method of inhibiting the change of a tumor in a subject from a dormant tumor or a benign tumor to a malignant tumor. The second claim set, Claims 30-33, is directed to a method of inhibiting genetic alteration of a tumor in a subject from a dormant tumor or a benign tumor to a malignant tumor. Therefore, three different claim sets are now pending in the present application, Claims 16, 17, 19, 24 and 25, Claims 26-29 and Claims 30-33. Upon the indication that a particular claim set is allowable, Applicants will cancel the remaining claim sets.

Claim 25 has been rejected under 35 USC 112, second paragraph, as being indefinite. Claims 16-19 and 24 have been rejected under 35 USC 103(a) as being unpatentable over Ginoux in view of Postaire et al, Takenaga et al, vanRossen et al and Das et al. Applicants respectfully request reconsideration in light of the following comments.

A first claim set of the present invention is directed to a method of inhibiting the malignant progression of a tumor in a subject comprising the steps of administering to the subject in which the malignant progression is to be inhibited a pharmacologically effective amount of a superoxide dismutase combined with gliadin.

A second claim set of the present invention is directed to a method inhibiting the change of a tumor in a subject from a dormant tumor or a benign tumor to a malignant tumor which comprises the steps of administering to the subject in which the malignant progression is to be inhibited a

pharmacologically effective amount of a superoxide dismutase combined with gliadin.

A third claim set of the present invention is directed to a method of inhibiting genetic alteration of a tumor in a subject from a dormant tumor or a benign tumor to a malignant tumor which comprises the steps of administering to the subject in which the genetic alteration is to be inhibited a pharmacologically effective amount of a superoxide dismutase combined with gliadin.

With respect to the Examiner's rejection of Claim 25 under 35 USC 112, second paragraph, Applicants appreciate the Examiner's discussion regarding a benign tumor not progressing malignantly, in the sense of malignant growth and spreading, i.e., metastasis. Applicants offer the following comments. Metastasis, as defined in "Medline Plus Medical Encyclopedia" is the movement or spreading of cancer cells from one organ or tissue to another. Cancer cells usually spread via the bloodstream or the lymph system. In contrast thereto, progression is described in the following manner. "The initiation and progression of human neoplasia is a multi-step process involving the accumulation of genetic changes in somatic cells." The preceding description is from "Holland/Frei's Cancer Medicine". A copy of this description is enclosed herewith for the Examiner's benefit.

"Progression" is used to express the genetic aspect or transformation of a tumor cell while the word "metastasis" is used to express a behavioral aspect of a tumor cell. The progression of a tumor is not the same as the growth or metastasis of a tumor. None of the references of record in the present application concluded that the experiments shown there inhibited malignant progression. In all of the experimental systems adopted by vanRossen, Das, and Takenaga, tumor growth (vanRossen, Das) or metastasis (Takenaga) were evaluated in animals which were administered respective agents (RBC component by vanRossen, PC-SOD by Takenaga, tea by Das). In these experimental systems, treatments influenced both the

body of the animal and also the tumor. Therefore, it cannot be said that the observed inhibitory effects were based on the effect to the host side or tumor side or on both the host and tumor side.

In contrast to the experimental systems and the references cited by the Examiner, in the experimental system of the present invention, as described in Table 1 of the specification, the character of a tumor cell developed in the host treated with SOD-G (Experiment A) was further studied in a normal animal by intravenous injection in Experiment B. By comparing the character of the original tumor cells with the treated ones in Experiment A, the change in character of the tumor cells in Experiment A was evaluated. Accordingly, the experimental system of Experiment B elucidated a genetic change that happened only in the tumor cells. As such, it is respectfully submitted that the prior art cited by the Examiner does not disclose the presently claimed invention.

Ginoux et al discloses the use of a soluble *Cucumis melo* protein extract having a superoxide dismutase enzyme activity for cosmetic purposes, medical purposes, such as anti-cancer agents for the digestive system and as an antioxidant, and food purposes such as the replacement of synthetic antioxidants. The orally administered SOD in this reference contacts directly with tumors located in the digestive track before inactivation thereof by proteinases contained in the digestive juices. This reference has no disclosure with respect to inhibiting the malignant progression or change of a tumor in a subject from a dormant tumor or a benign tumor to a malignant tumor through the administration of SOD-G.

Postaire et al discloses pharmaceutical compositions that are suitable for orally administering superoxide dismutases which are used in the treatment of inflammatory processes and toxic conditions associated with the presence of substantial amounts of oxygen. Although this reference discloses that superoxide dismutases can be administered with prolamines, such as gliadin, nothing in this reference suggests that the

malignant progression, genetic alteration or change of a tumor from a dormant tumor or a benign tumor to a malignant tumor can be inhibited through the administration of SOD-G.

Takenaga et al examines the effect of lecithinized SOD on experimental pulmonary metastasis in mice. However, this reference also has no disclosure with respect to inhibiting the malignant progression, change or genetic alteration of a benign tumor or a dormant tumor to a malignant tumor through the administration of SOD-G.

vanRossen et al shows the diminishing of peritoneal tumor reoccurrence by the scavenging of reactive oxygen species. Nothing in this reference suggests the inhibition of the change, malignant progression or genetic alteration of a tumor from a dormant tumor or a benign tumor to a malignant tumor by the administration of SOD-G.

Das et al examines the "effect" of tea consumption on the inhibition of tumor growth and inflammation. Like the previously discussed references, there is no disclosure in this reference regarding the inhibition of the change, malignant progression or genetic alteration of a tumor from a dormant tumor or a benign tumor to a malignant tumor through the administration of SOD-G.

None of the previously discussed references, either singularly or in combination, presents a showing of prima facie obviousness under 35 USC 103(a) of the presently claimed invention. However, as pointed out previously, there is objective evidence of record in the present application which is more than sufficient to rebut any proper showing of prima facie obviousness under 35 USC 103. In the Declaration Under 37 CFR 1.132 of record in the present application, the oral administration of SOD-G is compared with the oral administration of melon SOD for inhibiting the malignant progression of human colonic adenoma cells. Table 5 in the Declaration illustrates that the oral administration of SOD-G to mice effectively inhibited the malignant progression of human colonic adenoma in the mice while the oral

administration of melon SOD had no effect. This is clearly surprising and unexpected in light of the references cited by the Examiner and further establishes the patentability of the presently claimed invention.

The Examiner is respectfully requested to reconsider the present application and to pass it to issue.

Respectfully submitted,

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Encl: Description from Holland/Frei's Cancer Medicine
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